

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Cancelled).

2. (Previously Presented) The method of claim 6, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblast proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

3. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoblasts is:

1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

2) Bone specific alkaliphosphatase and osteocalcin.

4. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoclasts is a marker associated with bone type I collagen.

5. (Previously Presented) The method according to claim 6, wherein the marker that reflects the activity of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

6. (Previously Presented) In a method of diagnosing amelioration and/or exacerbation of metastasis of malignant tumor to bone in a patient with a cancer disease, using markers for bone formation that reflect the activity of osteoblasts and markers that reflect the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

a) a marker associated with the phase of calcification, and

b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from said patient for a
marker of bone metabolism,

wherein the amelioration of bone metastasis or
therapeutic effect and the degree of the exacerbation of bone
metastasis are diagnosed by monitoring said markers,

the improvement wherein said testing comprises
measuring for bone formation by measuring both (1) osteocalcin
and (2) at least one marker selected from the group consisting
of BALP, PICP and PINP, and

measuring bone resorption by measuring for ICTP,
determining a Z value for each of said osteocalcin
and said marker, each said Z value being determined by
dividing the difference between said measured value for said
patient and an average value for patients without bone
metastasis, by a standard deviation of a patient without bone
metastasis, and determining a crossover index by dividing said
Z value for osteocalcin by said Z value for BALP, PICP or
PINP,

determining ICTP level,
assessing amelioration and/or exacerbation of
metastasis in comparison with existing control data for CR,
PD, IMP and/or NC,

diagnosing amelioration and/or exacerbation based on
the value of said crossover index,

said crossover index and said ICTP level providing a diagnosis of progression of bone metastasis in the treatment of said patient for said cancer.

Claim 7 (Cancelled).

8. (Currently Amended) In a method of evaluating the efficacy of drugs for treatment of a cancer disease,

~~using at least one of~~ a formative marker that reflects the activity of osteoblasts ~~or at least one of~~ a marker that reflects the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

a) a marker associated with the phase of calcification, and

b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from a patient for a marker of bone metabolism,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said markers

the improvement wherein said testing comprises measuring for both (1) osteocalcin and (2) one marker selected from the group consisting of BALP, PICP and PINP, and

measuring bone resorption by measuring for ICTP, determining a Z value for each of said osteocalcin and said marker, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP, PICP or PINP,

determining ICTP level, assessing amelioration and/or exacerbation of metastasis in comparison with existing control data for CR, PD, IMP and/or NC,

diagnosing amelioration and/or exacerbation based on the value of said crossover index,

said crossover index and said ICTP level providing a diagnosis of progression of bone metastasis and evaluation of drug efficacy in the treatment of said patient for said cancer;

wherein a ~~layer~~ higher crossover index indicates amelioration of the patient's condition.

9. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a cancer control therapeutic agent.

10. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a bone resorption suppressant.

11. (Previously Presented) The method according to claim 8, wherein the drug evaluated is an endocrine therapeutic agent.

12. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblast proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

13. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) Bone specific alkaliphosphatase and osteocalcin.

14. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoclasts is a marker associated with bone type I collagen.

15. (Previously Presented) The method according to claim 8, wherein the marker that reflects the activity of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

Claims 16-24 (Cancelled).

25. (Previously Presented) The method according to claim 6 or 8, wherein said cancer disease is prostate cancer.

26. (Previously Presented) The method according to claim 6 or 8, wherein said cancer disease is breast cancer.

27. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a cancer control therapeutic agent.

28. (Previously Presented) The method according to claim 8, wherein the drug evaluated is a bone resorption suppressant.

29. (Previously Presented) The method according to claim 8, wherein the drug evaluated is an endocrine therapeutic agent.

30. (Previously Presented) In a method of evaluating the efficacy of a drug for the treatment of cancer or for the inhibition or amelioration of a metastasis of said cancer to bone in a patient with cancer, wherein said cancer is selected from the group consisting of prostate cancer and breast cancer,

the improvement wherein said testing comprises measuring for both (1) osteocalcin and (2) one marker selected from the group consisting of BALP, PICP and PINP,

determining a Z value for each of said osteocalcin and said BALP, PICP or PINP, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP, PICP or PINP,

said crossover index providing a diagnosis of progression of bone metastasis and evaluation of drug efficacy in the treatment of said patient for said cancer;

wherein assessing or judging amelioration and/or exacerbation of metastasis with regard to the Z value is carried out in comparison with data for CR, PD, IMP and/or NC.

Claim 31. (Cancelled).

32. (Currently Amended) In a method of evaluating the efficacy of a drug for the treatment of cancer or the inhibition or amelioration of a metastasis of said cancer to bone in a patient with cancer, wherein said cancer is prostate cancer or breast cancer,

the improvement wherein said evaluation comprises ~~testing serum of said patient for a marker of bone formation,~~

testing said serum for a marker of bone resorption, said marker for bone resorption comprising ICTP,

expressing measured values in terms of average and standard error,

analyzing variants (ANOVA) according to the Bonferroni method,

whereby ICTP values over time demonstrate progression of disease.

33. (New) In a method of diagnosing amelioration and/or exacerbation of metastasis of malignant tumor to bone in a patient with breast cancer,

using markers that reflect the activity of osteoblasts and markers that reflect the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

(a) a marker associated with the phase of calcification, and

(b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from said patient for a marker of bone metabolism,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed by monitoring said markers,

the improvement wherein said testing comprising measuring for both osteocalcin and BALP,

determining a Z value for each of said BALP and osteocalcin, each said Z value being determined by dividing

the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP, said crossover index providing a diagnosis of progression of bone metastasis in the treatment of said patient for breast cancer.

34. (New) In a method of evaluating the efficacy of drugs for treatment of breast cancer,

using a formative marker that reflects the activity of osteoblasts and a marker that reflects the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

(a) a marker associated with the phase of calcification, and

(b) a marker associated with the phase of osteoblasts proliferation and/or matrix formation,

2) wherein the marker that reflects the activity of osteoclasts is a marker associated with osteoclasts targeted to evaluation of worsening of the disease,

comprising testing blood from said patient for a marker of bone metabolism,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said markers, the improvement wherein said testing comprises measuring for both osteocalcin and BALP,

determining a Z value for each of said osteocalcin and said BALP, each said Z value being determined by dividing the difference between said measured value for said patient and an average value for patients without bone metastasis, by a standard deviation of a patient without bone metastasis, and

determining a crossover index by dividing said Z value for osteocalcin by said Z value for BALP,

said crossover index providing a diagnosis of progression of bone metastasis and evaluation of drug efficacy in the treatment of said patient for said cancer; wherein a higher index indicates amelioration of the patient's condition.

35. (New) A method of evaluating the degree of exacerbation of cancer metastasis to bone, comprising testing blood from a patient with cancer disease for ICTP determining the ICTP level, wherein a higher ICTP level indicates exacerbation of cancer metastasis to bone.

36. (New) The method according to claim 35,
wherein the cancer disease is breast cancer.